Inherited retinal diseases

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CHAPTER 14

VALORISATION

“Who would believe that so small a space could contain the images of all the universe?”

LEONARDO DA VINCI

Of all the fields of Medicine, advances in technology have impacted Ophthalmology most. The world of retinal diseases is no exception. Vitreoretinal diseases that would have been deemed 'inoperable' a few years ago are routinely being done; retinal diseases that never would have been diagnosed, let alone treatable- are being diagnosed with Spectral domain optical coherence tomography (SD-OCT), OCT-Angiography, adaptive optics, microperimetry and treated- with the advent of micro incision vitrectomy surgery for example advanced diabetic tractional retinal detachments, stage 5 retinopathy of prematurity and complex traumas

Genetic diseases of the retina continue to frustrate clinicians (and patients) alike, as they are not amenable to conventional medical or surgical treatment. There is a ray of hope however tenuous at the present time, with the recent approval of gene therapy for RPE-65 related retinal dystrophies, and despite the multiple clinical trials ongoing around the world, the world is still a dark place for patients with these diseases.

As I sat in the outpatient of the retina clinic many years ago, I saw this consanguineous couple with a young child, who had progressive visual failure and seizures. Over the next few weeks, as we informed the mother of the diagnosis of Batten's disease (Neuronal ceroid Lipofuscinosis) in her child, the mother had a question: This was her fourth child; she now had three of her four children affected with this blinding and fatal condition. Why hadn't any doctor told her about this before? Could we have prevented this condition in her children? In chapter 8 the basis for this opportunity to diagnose Neuronal ceroid Lipofuscinosis based on exome sequencing is described.

This opened up the world of 'retinal dystrophies' and 'ophthalmic genetics' to me. As I got more interested, I began to see more and more patients with degenerative diseases of the retina.

My journey into the fascinating world of retinal dystrophies had begun. I knew this was an area of research that I wanted to pursue.

Retinitis pigmentosa is the commonest retinal dystrophy. The prevalence of RP in India is more than 1 in 1000, compared to that of 1 in 4000 in the USA. That puts the number at close to 1.5 million affected with RP alone in India. This is not even considering other retinal dystrophies like Stargardt disease or LCA. Based on the prevalence alone this was then a socially relevant problem to study. Moreover, it supports the need to study this genetic disease from an Indian perspective and also find specific genetic mutations/ modifier genes fueled also by a high prevalence of consanguinity.

Was my study **economically relevant?** Undoubtedly. While there are several programs like the National Program for Control of Blindness, "orphan" diseases like retinal dystrophies receive very little attention. For every person who is blind, there are three people who are visually impaired. The economic burden of blindness in India for the year 1997 was Rs.159 billion (US$ 4.4 billion). While 23.5 % of the blind in the world live in India, there are no definite statistics about blindness/visual impairment due to retinal degenerative diseases. [1,2]

As I grappled to understand these diseases better, recent technological advances helped me get a better understanding of them. Looking at cone photoreceptors through Adaptive optics or getting better understanding of the blood flow in RP through Oximetry opened up newer insights into the pathogenesis of these diseases as described in *Chapters 3* to *6*. It now is possible to see the photoreceptors in vivo and study its density in RP. OCT also gave the opportunity to study the retina in much more detail in vivo in a detail almost similar to that achieved by histological examinations. Moreover, we are now better informed about the relation between the structural changes in Adaptive optics and OCT the function. The latter improved by micro-perimetry as compared to traditional perimetry. Microperimetry shows the sensitivity at a local point and at more points in the center and the opportunity to assess the sensitivity value in exactly the same place after some follow-up time. The sensitivity can therefore be closely related to the local changes in OA and OCT in the same spot.

As disease progression occurs in retinal dystrophies, the retinal tissue reacts to the injury in several ways; one of them is the formation of outer retinal tubules (ORT) described on the SD-OCT. I was curious to see how these tubules appeared on the adaptive optics; whether we could image them at all. Doing simple mathematical calculations based on the location of the ORTs on the SD-OCT, we identified possible locations of the tubules on the Adaptive optics; it was an exciting moment to see long tubules on stitched images of Adaptive Optics as is described in *Chapter 4*. It had not yet been described in Bietti's Crystalline Dystrophy.

As we started conducting molecular genetic tests on the families presenting at our hospital, it became increasingly clear that there was limited information in the Indian literature regarding retinal dystrophies. While ophthalmic research is at the forefront in India, insights into the molecular genetics of retinal dystrophies was lacking. Towards this end, we published a series of mutations, both already noted and some new to add to the world literature *(Chapters 7-9)*. Managing the staggering number of patients in the genetic clinic brought fore the difficulties associated. *(Chapter 10)* Although we now had clinicians trained in managing patients with IRDs, there were no trained genetic counselors. Managing these patients and their families amidst a busy retina clinic was a challenge in itself. There were very few laboratories that were doing genetic mutational work in IRDs. Talking to multiple labs, discussing with them the importance of starting to look at eye/retina related genes, correlating them to the clinical phenotype- all taught me invaluable lessons.

At Narayana Nethralaya, we hosted a two-day international symposium titled 'SIGN-Symposium on Inherited Retinal Disease, Genetics and Newer treatments in 2013. This was a combination of presentations in basic genetics and clinical discussions. We were fortunate to have world leaders in the field of Ophthalmic Genetics come and address the sessions. And I continued to learn!

There is a surge in research into retinal dystrophies in the last decade. This thesis adds significantly to the existing literature about retinal dystrophies in India. With the many elements of research – be it gene therapy, stem cell research, retinal prostheses, small molecules, pharmaceutical therapy- we need more data about the spectrum of retinal dystrophies in India and its impact on the affected people. Once more data is gathered on the clinical phenotype, the number of affected people, the specific genetic mutations in the Indian population- it is then possible to start focusing on the therapies possible. Clinical trials in IRDs can then be started in India to look at multiple treatment options.

Retinal prostheses- both epiretinal and subretinal have been approved for use today.[3] The USFDA approval of Luxturna- voretigene neparvovec-rzyl for RPE-65 disease developed by Spark therapeutics, USA is a very exciting landmark in the treatment of retinal dystrophies. However, gene therapy poses a very expensive prospect for affected patients. Each injection of Luxturna costs over $450,000 per injection currently in the United States. Although no patient in India has received either of these treatments yet, the development of both retinal prosthesis and gene therapy product is a remarkable achievement for science. In addition, both these therapies can behave like platform technologies based on which further products can be developed.

There are several ophthalmic institutions in India doing research in this area - RP Centre for Ophthalmic Sciences, New Delhi, LV Prasad Eye Institute, Hyderabad, Sankara Nethralaya, Chennai, Aravind Eye Hospitals, Madurai, Narayana Nethralaya, Bangalore.

My own research has grown beyond the scope of this thesis. The Centre for Eye Genetics and Research in Bangalore *(www.cegr.org)* has been established with the sole idea of managing patients with retinal dystrophies, and provide the time and professional care these patients deserve. Services provided at CEGR include comprehensive clinical examination to arrive at a correct phenotype, genetic counseling after molecular genetic testing, clinical genetic services, personalized low visual rehabilitation services and collaboration with other organizations like ORDI (Organization for Rare Diseases India). Along with ORDI, CEGR has been organizing 'Racefor7', an annual marathon to raise awareness about rare diseases of the eye.

What began as a small idea about exclusive management of these patients turned out to be the beginning of 'Eyestem' *(www.eyestem.com)*. Eyestem is a retinal stem cell company that focuses on research into retinal degenerative diseases. It is incubated at CCamp (Centre for Cellular and molecular platforms), within the NCBS (National Centre for Biological Sciences) campus, Bangalore, India. Eyestem boasts of a dedicated set of scientists and an exceptional advisory team.

The goal of the company is to be able to replace defective photoreceptors and retinal pigment epithelium in patients with retinal degenerative diseases. Towards this, we have used induced pluripotent stem cells (iPSC) from peripheral blood and differentiated them into Retinal Pigment Epithelium (RPE) and photoreceptors (PR) invitro.[4] Our first set of animal experiments in dedicated knock out models has begun and we have shown successful integration of RPE cells transplanted subretinally.

Autologous stem cell treatment is possible; however the cell lines naturally carry the same genetic mutation that is in the eye. The combination of iPSC and remarkable genome editing tools like CRSIPR/Cas-9 (Clustered Regularly Interspaced Short Palindromic Repeats) make personalized therapy a reality, where a patient's own cells are corrected and used to replace their degenerating retina.[5] However this is bound to be a challenging and expensive proposition.

Allogeneic stem cell treatment seems an attractive option to autologous treatment. Although the eye is considered immune-privileged, immune responses is one of the major hurdles for allogenic therapy. Systemic and local immunosuppression is administered in current trials; this research is still in its early stages. HLA matched allogeneic stem cell banks that are able to produce clinical grade cells seems a definite possibility.

At Eyestem, we are aware of challenges ahead. Some of these include overcoming immune responses, difficulties associated with integration of our cells within the host retina, clinical challenges of identifying critical end points in the disease and subretinal administration of the cells and associated regulatory hurdles. However, as science stands at the cusp of major breakthroughs in all these areas across the world, we are quite hopeful that we should be able to bring our current research to the bedside and be able to treat the many affected patients.

To quote the famous French mathematician François Arago

"To get to know, to discover, to publish- this is the destiny of a scientist"

Suggested Reading

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4. *Rathod R, Surendran H, Battu R, Desai J, Pal R. Induced pluripotent stem cells (iPSC)-derived retinal cells in disease modeling and regenerative medicine. J Chem Neuroanat. 2018 Feb 12. pii: S0891-0618(17)30120-5.*
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